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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/003,354	12/06/2001	C. Frank Bennett	RTS-0348	5827

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EXAMINER
GIBBS, TERRA C

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 09/11/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/003,354	BENNETT ET AL.	
	Examiner	Art Unit	
	Terra Gibbs	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 August 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2 and 4-20* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2 and 4-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 3 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Preliminary Amendment A, filed 8/27/02, in Paper No. 4 is acknowledged. Claim 3 has been canceled. Claims 1, 2 and 4-20 are pending in the instant application.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 15-18 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a compound 8 to 50 nucleobases in length that hybridizes with and inhibits the expression of phosphatidylinositol-4-phosphate 5-kinase Iα *in vitro*, does not reasonably provide enablement for a method of inhibiting the expression of phosphatidylinositol-4-phosphate 5-kinase Iα in tissues (*in vivo*) as in claim 15 or a method of treating an animal having a disease or condition associated with phosphatidylinositol-4-phosphate 5-kinase Iα as in claims 16-20. The specification does not enable any person of ordinary skill in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claims 15-18 are drawn to or embrace an antisense-based therapy in an animal having a disease or condition associated with phosphatidylinositol-4-phosphate 5-kinase Iα via a compound 8 to 50 nucleobases in length that hybridizes with and inhibits the expression of phosphatidylinositol-4-phosphate 5-kinase Iα.

The instant invention specification provides methodologies for antisense inhibition of phosphatidylinositol-4-phosphate 5-kinase Iα in cell culture.

The specification as filed does not provide adequate guidance of examples that would show by correlation the practice of the instant invention without the need for undue trail and error experimentation. The specification as filed contemplates the therapeutic use of phosphatidylinositol-4-phosphate 5-kinase Iα antisense in a broad range of diseases (e.g. hyperproliferative disorders and inflammatory disorders). However, the instant specification does not show any specific link to phosphatidylinositol-4-phosphate 5-kinase Iα and any specific disease such that treatment with phosphatidylinositol-4-phosphate 5-kinase Iα would be an apparent treatment option, without undue trial and error experimentation, for example. How does one in the art correlate the cell culture (*in vitro*) data to treat a particular disease (*in vivo*) with phosphatidylinositol-4-phosphate 5-kinase Iα? (i.e. this would require different modes of treatment where no specific guidance is provided for any particular disease).

The unpredictability of the art of antisense therapy in general adds to the lack of enablement for the current invention. For example, Branch (TIBS Vol. 23, February 1998) addresses the unpredictability and the problems faced in the antisense art with the following statements: "Antisense molecules and ribozymes capture the imagination with their promise or rational drug design and exquisite specificity. However, they are far more difficult to produce than was originally anticipated, and their ability to eliminate the function of a single gene has never been proven."; "To minimize unwanted non-antisense effects, investigators are searching for antisense compounds and ribozymes whose targets sites are particularly vulnerable to attack. This is a challenging quest."; "However, their unpredictability confounds research application of

nucleic acid reagents."; "Non-antisense effects are not the only impediments to rational antisense drug design. The internal structures of target RNAs and their associations with cellular proteins create physical barriers, which render most potential binding sites inaccessible to antisense molecules."; "Years of investigation can be required to figure out what an 'antisense' molecule is actually doing,..."; "Because knowledge of their underlying mechanism is typically acting, non-antisense effects muddy the waters."; "Because biologically active compounds generally have a variety of effects, dose-response curves are always needed to establish a compounds primary pharmacological identity. Antisense compounds are no exception. As is true of all pharmaceuticals, the value of a potential antisense drug can only be judged after its intended clinical use is known, and quantitative information about its dose-response curve of conventional drugs, which typically span two to three orders of magnitude, those of antisense drugs, extend only across a narrow concentration range."; "Because it is very difficult to predict what portions of an RNA molecule will be accessible *in vivo*, effective antisense molecules must be determined empirically by screening large number of candidates for their ability to act inside cells."; "Binding is the rare exception rather than the rule, and antisense molecules are excluded from most complementary sites. Since accessibility cannot be predicted, rational design of antisense molecules in not possible."; and, "The relationship between accessibility to oligonucleotide (ODN) binding and vulnerability to ODN-mediated antisense inhibition *in vivo* is beginning to be explored...It is not yet clear whether *in vitro* screening techniques...will identify ODN's that are effective *in vivo*."

Jen et al. (Stem Cells, 2000, Vol. 18:307-319) discuss antisense-based therapy and the challenges that remain before the use of antisense becomes routine in a therapeutic setting. Jen

et al. discuss the advances made in the art but also indicate that more progress needs to be made in the art. In the conclusion of their review, Jen et al. assert, "Given the state of the art, it is perhaps not surprising that effective and efficient clinical translation of the antisense strategy has remained elusive." It is also stated "The key challenges to this field have been outlined above. It is clear that they will have to be solved if this approach to specific antitumor therapy is to become a useful treatment approach. A large number of diverse and talented groups are working on this problem, and we can all hope that their efforts will help lead to establishment of this promising form of therapy." It is clear from Jen et al. that the state of the art of antisense is unpredictable and those highly skilled in the art are working towards making the art of antisense therapy more predictable but have many obstacles to overcome.

It would appear that in view of the above, one of ordinary skill in the art would require specific guidance on how to practice the current invention. The current specification does not provide such guidance and one of ordinary skill in the art would be required to perform undue trail and error experimentation to practice the current invention. The quantity of undue experimentation would include overcoming the obstacle to routine antisense therapies as exemplified in the references discussed above. In addition, the quantity of undue experimentation would include the modes of treatment selected from the range of diseases contemplated (e.g. hyperproliferative disorders and inflammatory disorders), for example.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 2, 4-14 and 19 and 20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Honda et al. (Cell, 1999 Vol. 99: 521-532) Loijens et al. (Journal of Biological Chemistry, 1996 Vol. 271:32937-32942), in further view of Weintraub (Scientific American, 1990 pages 40-46) Baracchini et al. [U.S. Patent No. 5801154] and Fritz et al. (Journal of Colloid and Interface Science, 1997 Vol. 195:272-288).

Claims 1, 2 and 4-14 are drawn to a compound 8 to 50 nucleobases in length targeted to a nucleic acid molecule encoding phosphatidylinositol-4-phosphate 5-kinase Iα; wherein said compound specifically hybridizes with said nucleic acid molecule encoding phosphatidylinositol-4-phosphate 5-kinase Iα and inhibits the expression of phosphatidylinositol-4-phosphate 5-kinase Iα; wherein the compound is an antisense; wherein the antisense oligonucleotides comprises at least one modified internucleoside linkage; wherein the modified internucleoside linkage is a phosphorothioate linkage; wherein the antisense oligonucleotide comprises at least one modified sugar moiety; wherein the sugar moiety is a 2'-O-methoxyethyl sugar moiety; wherein the antisense oligonucleotide comprises at least one modified nucleobase; wherein the modified nucleobase is a 5-methylcytosine; wherein the

antisense oligonucleotide is a chimeric oligonucleotide; and a composition comprising the compound of claim 1 and a pharmaceutically acceptable carrier or diluent, further comprising a colloidal dispersion system. Claim 19 is drawn to the compound of claim 1 targeted to a nucleic acid molecule encoding phosphatidylinositol-4-phosphate 5-kinase Iα, wherein said compound specifically hybridizes with and differentially inhibits the expression of one of the variants of phosphatidylinositol-4-phosphate 5-kinase Iα relative to the remaining variants of phosphatidylinositol-4-phosphate 5-kinase Iα. Claim 20 is drawn to the compound of claim 19 targeted to a nucleic acid molecule encoding phosphatidylinositol-4-phosphate 5-kinase Iα wherein said compound hybridizes with and specifically inhibits the expression of a variant phosphatidylinositol-4-phosphate 5-kinase Iα, wherein said variant is selected from the group consisting of PIP5KIα1, PIP5KIα2 and PIP5KIα3.

Honda et al. teach phosphatidylinositol-4-phosphate 5-kinase Iα is a downstream effector of the small G-protein, ARF6. Honda et al. further teach a novel physiological function of phosphatidylinositol-4-phosphate 5-kinase Iα in the involvement of membrane ruffle formation (see page 529, first paragraph).

Loijens et al. teach PIP5KIα2 and PIP5KIα3 as splice variants of PIP5KIα1. Loijens et al. also teach that the isolation of the first PIPk5I cDNA has shown them to be distinct members of the same lipid kinase family and permits comparative studies of these isoforms (see page 32492, last paragraph). Loijens et al. further teach a role for PIP5Ks, including PIP5KIα1, PIP5KIα2 and PIP5KIα3, in regulated secretion, cytoskeletal dynamics and signaling cascades (see page 32942, last paragraph).

Honda et al. and Loijens et al. do not teach a nucleic acid molecule encoding phosphatidylinositol-4-phosphate 5-kinase Iα which hybridizes with and inhibits the expression of phosphatidylinositol-4-phosphate 5-kinase Iα or a phosphatidylinositol-4-phosphate 5-kinase Iα antisense. Honda et al. and Loijens et al. do not teach antisense oligonucleotides comprising at least one modified internucleoside linkage; wherein the modified internucleoside linkage is a phosphorothioate linkage; wherein the antisense oligonucleotide comprises at least one modified sugar moiety; wherein the sugar moiety is a 2'-O-methoxyethyl sugar moiety; wherein the antisense oligonucleotide comprises at least one modified nucleobase; wherein the modified nucleobase is a 5-methylcytosine; wherein the antisense oligonucleotide is a chimeric oligonucleotide; and a composition comprising the compound of claim 1 and a pharmaceutically acceptable carrier or diluent, further comprising a colloidal dispersion system.

Weintraub teach antisense nucleic acids as molecules that bind with specific messenger RNA's to turn off genes. Weintraub also teaches antisense techniques as a tool for probing the functions of individual genes (see page 41). Weintraub further teaches, "antisense RNA molecules can selectively inhibit the activity of genes and block the production of specific proteins in living cells" (see page 41).

Baracchini et al. teach, "oligonucleotides are designed to bind either directly to mRNA or to a selected DNA portion forming a triple stranded structure, thereby modulating the amount of mRNA made from the gene"... "the relationship between an oligonucleotide and its complementary target nucleic acid is commonly denoted as antisense"... "it is preferred to target specific genes for antisense attack"... (see column 3, lines 17-41). Baracchini et al. further teach modified or substituted oligonucleotides are often preferred over native forms because of

desirable properties such as enhanced cellular uptake, enhanced affinity for nucleic acid target and increased stability in the presence of nucleases. Baracchini et al. finally teach antisense oligonucleotides with phosphorothioate modified backbones (see column 6, line 37)... with at least one modified sugar moiety and a modified 2'-O-methoxyethyl sugar moieties (see Table I)... with modified nucleobases, such as 5-methylcytosine (see column 7, lines 15-25). Baracchini et al. finally teach an antisense oligonucleotide as a chimeric oligonucleotide (see column 8, lines 12-19)

Fritz et al. teach a composition comprising an antisense oligonucleotide and a pharmaceutically acceptable carrier or diluent comprising a colloidal dispersion system. Fritz et al. further teach that oligonucleotides, in combination with steric stabilizers, exhibit high colloidal stability with low toxic side effects as required for biological experiments in cell culture and *in vivo* (see page 287, last paragraph).

One of ordinary skill in the art would have been motivated to make antisense nucleic acids targeting phosphatidylinositol-4-phosphate 5-kinase Iα since the prior art taught phosphatidylinositol-4-phosphate 5-kinase Iα involvement in membrane ruffle formation, regulated secretion and signal transduction (Honda et al. and Loijens et al.). One of ordinary skill in the art would have been motivated to inhibit the expression of one phosphatidylinositol-4-phosphate 5-kinase Iα variant over another since Loijens et al. taught PIP5KIα2 and PIP5KIα3 as splice variants of PIP5KIα1 which permit comparative studies of each isoforms. It would have been obvious to make antisense oligonucleotides encoding phosphatidylinositol-4-phosphate 5-kinase Iα since Weintraub taught antisense nucleic acids can selectively inhibit the activity of genes and gene expression and antisense techniques are tools for probing the functions

of individual genes. One of ordinary skill in the art would have been motivated and had a reasonable expectation of success in modifying antisense oligonucleotides since the prior art has taught the desirability of such oligonucleotides are often preferred over native forms because of enhanced cellular uptake, enhanced affinity for nucleic acid target, increased stability in the presence of nucleases and the exhibition of high colloidal stability with low toxic side effects as required for biological experiments (Baracchini et al. and Fritz et al.).

The invention as a whole would therefore have been obvious to one of ordinary skill in the art at the time the invention was made.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Terra C. Gibbs whose telephone number is (703) 306-3221. The examiner can normally be reached on M-F 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on (703) 308-0447. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 746-8693 for regular communications and (703) 872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

tcg
September 9, 2002

SEAN McGARRY
PRIMARY EXAMINER
1635